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A multivitamin infusion prevents lipid peroxidation and improves transplantation performance

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A multivitamin infusion prevents lipid peroxidation and improves transplantation performance. The objective of this study was to test the hypothesis that ischemia reperfusion damage in kidney transplantation is associated with lipid peroxidation and that inhibition of lipid peroxidation by antioxidants improves the function of the transplanted kidney. Lipid peroxidation was assessed by measuring the plasma malonaldehyde content (as thiobarbituric acid reaction product) with high-performance liquid chromatography. Kidney function was assessed by plasma creatinine and creatinine clearance. Thirty patients of an ongoing series were randomly selected into two groups, with 14 controls and 16 patients in the antioxidant therapy group. Therapy consisted of two ampoules of Omnibionta (which contains vitamins C, E, A and B complex) diluted in 500 ml physiological sodium chloride, which was infused intravenously prior to reperfusion onset. No significant differences existed for the age of the patients in the control (43.00 ± 9.86 years) and the therapy group (41.56 ± 14.14 years) nor in the kidney preservation time, which was 24.12 ± 8.73 and 18.43 ± 9.97 hours in the control and therapy group, respectively. The controls showed a transient increase of plasma lipid peroxides as measured by malonaldehyde with a peak one hour after onset of reperfusion. Compared to the baseline value of 0.74 ± 0.26 (mean ± SD) the one hour malonaldehyde value increased to 1.46 ± 0.22 nmol/ml ($P < 0.001$). In the therapy group the plasma malonaldehyde level did not increase, but slightly decreased by about 20% compared to the baseline value. The difference of plasma malonaldehyde between the two groups one hour after reperfusion onset was highly significant ($P > 0.0001$). Compared to the control group, the therapy group had significantly lower creatinine values at the postoperative days 1, 2, 3 and 4 ($P < 0.02$, <0.006, <0.02 and <0.02, respectively). Also, the creatinine clearance rates were significantly higher in the therapy group on days 1, 3 and 5 ($P < 0.03$, <0.01 and <0.007). From day 6 on, no further improvement of creatinine and creatinine clearance occurred in the therapy group and no significant difference existed toward controls. This study shows that antioxidative treatment by vitamins could be an important regimen in the reduction of reperfusion damage.

Reactive oxygen species have been demonstrated by numerous investigators [1–6] as one of the main sources of post-ischemic injury. The kidneys appear to be relatively sensitive to reperfusion injury [7]. The involvement of lipid peroxidation induced by oxygen radicals has been strongly supported by studies of Paller et al [8, 9], although others have not been able to detect evidence for lipid peroxidation using similar experimental models [10, 11]. Lipid peroxidation has usually been assessed by measuring the amount of thiobarbituric acid reactive substances (malonaldehyde) present in plasma or the ischemic organ [12, 13].

Kidneys intended for transplantation are often subjected to both warm ischemia before or at the time of removal and reperfusion, and cold ischemia caused by preservation. While cold ischemia results in only moderate renal damage, as most metabolic functions are drastically reduced, warm ischemia leads to variable damage during harvesting of the organ and vascular reperfusion [14–17]. During ischemia an accumulation of xanthine oxidase and its substrate, hypoxanthine and xanthine have been demonstrated in several animal studies [16, 18, 19]. It has also been shown that allopurinol, a xanthine oxidase inhibitor, has a protective effect against ischemia-induced renal injury [7, 14, 20–22]. A number of lipid mediators have been proposed as modulators in ischemic/reperfusion injury. These include vasodilatory prostaglandins [23] as well as the vasoconstrictors thromboxane A2 [24], platelet activating factor [25] and expoxyeicosatrienoic acids [26]. Nath and Paller observed that animals chronically deficient in both selenium and α-tocopherol had greater functional impairment, histologic injury and lipid peroxidation after ischemia [27], and Paller and Patten found a readily apparent increase in H_2O_2 production in tubules subjected to anoxia and reoxygenation [28].

If oxygen radicals and lipid peroxidation have a causative role in reperfusion injury, then antioxidants should have a protective effect. The main antioxidant in biological membranes is α-tocopherol (vitamin E), which prevents lipid peroxidation [reviewed in 29, 30]. A protective effect of vitamin E has been reported for spinal cord injury [31], myocardial ischemia reperfusion injury [32] and ischemic rat liver cell injury [33]. Takenaka [34] demonstrated a protective effect of α-tocopherol on warm ischemic damage to rat kidney, where it led to an increase of ATP synthesis after reflow following warm ischemia and a lower serum creatinine level. This effect on metabolic function was also accompanied by an increase in the survival rate of ischemic rats. Yoshikawa et al [35] showed that gastric mucosal injury induced by ischemia reperfusion is more severe in vitamin E deficient rats as compared to vitamin E non-deficient rats. Vitamin C is a water soluble antioxidant which can detoxify oxygen radicals produced in the aqueous phase. In

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addition, vitamin C acts synergistically with vitamin E by recycling it at the membrane-water interphase [36, 37]. β-Carotene, known as provitamin A, is an efficient quencher for singlet oxygen and a similar effect has been ascribed to retinol and its derivatives [38].

We have previously shown in human patients that reperfusion following kidney transplantation or limb revascularization is associated with a strong lipid peroxidation process commencing shortly after onset of reperfusion and that it lasts for about one to two hours [39]. We now show that in kidney transplantation this lipid peroxidation can be prevented by intravenous infusion of Omnibionta, a multi-vitamin preparation containing antioxidants; this treatment also increases kidney viability and function.

Methods

Patients

The group of patients comprised 30 subjects (22 male, 8 female) with a mean age of 42.23 years (range 21 to 63), who were admitted to the Department of Urology at the University of Graz for kidney transplantation. The surgical procedure of kidney transplantation was performed according to the method of Hinman [40]. Peripheral venous blood samples were taken from each patient intraoperatively 30 minutes before and 1, 2, 3 and 4 hours and occasionally 6 to 18 hours after onset of reperfusion of the transplanted kidney. Blood samples were drawn without venous occlusion into EDTA-coated plastic tubes, the plasma was separated by centrifugation and stored at −20°C until analysis for lipid peroxidation (that is MDA-thiobarbituric acid adduct determined by HPLC) for no longer than 2 weeks. According to our experience, only minimal increase of MDA-TBA occurs in EDTA supplemented plasma during 2 weeks storage time at −20°C. Lee [41] found also nor significant increase in plasma samples supplemented with EDTA + GSH stored at 4°C for several weeks.

Out of the 30 patients in this study group 16 were randomly selected for treatment with Omnibionta (therapy group), whereas the remaining 14 patients not receiving Omnibionta but also receiving kidney allograft are considered in this study as controls. For treatment with Omnibionta, the content of two ampoules, 10 ml each, was diluted with 500 ml physiological sodium chloride solution. The infusion flask was covered by a dark paper to protect against light. Immediately after taking the first blood sample, that is, 30 minutes before onset of reperfusion, the diluted Omnibionta solution was administered intravenously and most of the solutions were infused before reperfusion of the implanted kidney was started.

Lipid peroxidation was assessed by plasma MDA levels. The collected and stored (−20°C) plasma samples were reacted with thiobarbituric acid and the MDA-thiobarbituric acid adduct was determined by HPLC as described by Wong et al [42], details of this procedure were reported by us elsewhere [39].

Plasma creatinine levels were determined routinuously daily up to day 9 after kidney transplantation according to [43]; creatinine clearance was determined according to [43] on days 1, 3, 5 and 7 after transplantation.

Omnibionta concentrate for infusion was from Merck (Darmstadt, Germany) and in Austria it has the registry number 13760. According to the accompanying information sheet, one ampoule (10 ml) contains: 5.5 mg retinol palmitate, 50.0 mg thiaminchloride-hydrochloride, 10.0 mg riboflavin 5-phosphate sodium, 100.0 mg nicotinamide, 25.0 mg dexpanthenol, 15.0 mg pyridoxin-hydrochloride, 500.0 mg ascorbate, 5.0 mg α-tocopherol-acetate, 150.0 mg benzylalcohol, 500.0 mg polysorbate 80, 1.0 mg DL-α-tocopherol, 200.0 mg propylenglycol, 2500.0 mg glycerin 85%, 360.0 mg trometamol and 10 ml water added.

Statistical analysis was performed by the nonparametric Mann-Whitney U-test.

Results

The study included 30 patients who underwent surgical revascularization operations for kidney transplantation. All 14 subjects of the control group after one hour of reperfusion showed a strong increase ($P < 0.001$) of plasma lipid peroxides (as measured by MDA) compared to the initial baseline value. The values returned to baseline again after about three to four hours (Table 1). The statistical mean values measured 30 minutes prior to reperfusion and 1, 2, 3 and 4 hours after reperfusion were 0.74, 1.46, 0.98, 0.91 and 0.77 nmol MDA/ml plasma. The time course of the mean change of the MDA values is shown in Figure 1. Occasionally measurements were also performed at later time points. One and two days after transplantation, the statistical mean was still at the baseline level. After three and four days, however, a second onset of lipid peroxidation appeared to occur, since six out of the seven patients examined had increased MDA values again.

As can be seen from the data in Table 2, treatment with Omnibionta inhibited the increase of MDA values. In 10 out of 16 patients, was after one hour of reperfusion the MDA equal to or even lower than the initial value measured prior to reperfusion. In the remaining six patients a weak increase of MDA was observed, but this was minimal as compared to the increase shown by the untreated control group (Table 1). The statistical mean values measured in the therapy group 30 minutes prior to reperfusion and 1, 2, 3 and 4 hours after reperfusion were 0.95, 0.86, 0.76, 0.76 and 0.74 nmol MDA/ml plasma, respectively. In the therapy group, statistically no significant difference exists between baseline measured prior to reperfusion and the values measured up to four hours after reperfusion. The time course of the change of the MDA values in the therapy group in comparison to the control group is shown in Figure 1. The difference of the percentual change between the control and the therapy group after one hour was statistically significant at $P < 0.0001$. In the therapy group, the MDA values remained more or less constant between one and four hours after kidney transplantation. At the third and fourth day after transplantation, four out of eight patients, who were further examined, showed increased MDA values again.

The time profile of serum creatinine in both groups is shown in Figure 2. Preoperative creatinine was nearly identical for the control and therapy group (9.70 vs. 9.97 mg/dl). In the control group creatinine was rather stable over two days after surgery, like the preoperative value, thereafter creatinine gradually decreased reaching a value of about 5.5 mg/dl at day 7. In the therapy group creatinine levels steadily decreased from the first to the sixth day after transplantation. During this period the creatinine was statistically significant ($P < 0.006$ to 0.02) lower than in the control group. From day 7 on both groups had more or less the same creatinine levels. That the therapy group had a

Table 1. MDA values determined by HPLC in plasma of patients receiving kidney allograft (control group)

Patient number	Age *years*	Kidney		MDA *nmol/ml plasma*								
		Preservation hr	Solution	−0.5 hr	1.0 hr	2.0 hr	3.0 hr	4.0 hr	1 day	2 day	3 day	4 day
1	42	18.3	EC	0.35	1.47	0.91	0.59	0.45	—	—	—	—
2	35	28.0	HTK	0.9	1.11	0.76	0.90	0.83	0.74	1.01	—	—
3	56	5.0	EC	0.9	1.29	1.37	1.22	0.83	0.93	1.15	1.43	1.11
4	33	29.2	HTK	0.32	1.40	0.38	0.53	0.48	0.51	0.37	0.48	0.80
5	33	28.2	EC	0.54	1.12	0.31	0.24	0.54	0.37	0.51	—	—
6	27	17.4	EC	0.55	1.50	0.72	0.86	0.53	—	—	—	0.53
7	56	28.5	HTK	1.20	1.71	1.25	1.01	0.85	0.93	0.64	—	—
8	35	12.2	UW	0.58	1.70	1.29	—	—	—	—	—	—
9	38	22.0	UW	0.76	1.31	0.80	0.81	0.80	0.58	0.53	0.80	—
10	42	28.0	EC	0.63	1.28	1.40	1.19	1.08	0.85	1.31	—	—
11	47	25.2	EC	1.09	1.84	1.22	1.17	1.28	—	—	—	—
12	56	34.0	UW	0.90	1.51	1.01	1.04	0.75	1.34	1.29	2.07	0.98
13	52	38.5	UW	0.83	1.62	0.97	0.90	0.79	0.85	0.80	1.20	1.25
14	50	23.2	UW	0.90	1.69	1.42	1.39	0.87	0.94	0.88	1.30	1.23
Mean	43.00	24.12		0.74	1.46[a]	0.98	0.91	0.77	0.80	0.85	1.21	0.98
±SD	9.86	8.73		0.26	0.22	0.36	0.31	0.23	0.27	0.33	0.54	0.27

This is a supplemented version of Table 1 in ref. 39. Blood samples were taken 0.5 hr prior to reperfusion and 1, 2, 3, 4 hours and 1, 2, 3 and 4 days after beginning reperfusion. Dash (—) means not determined. Given is also the preservation time of the transplanted kidney and the solution, in which it was kept prior transplantation. Abbreviations are: EC, Euro Collins; UW, University of Wisconsin; HTK, histidine-tryptophane-ketoglutarate.

[a] $P < 0.001$ compared to the 0.5 hr value

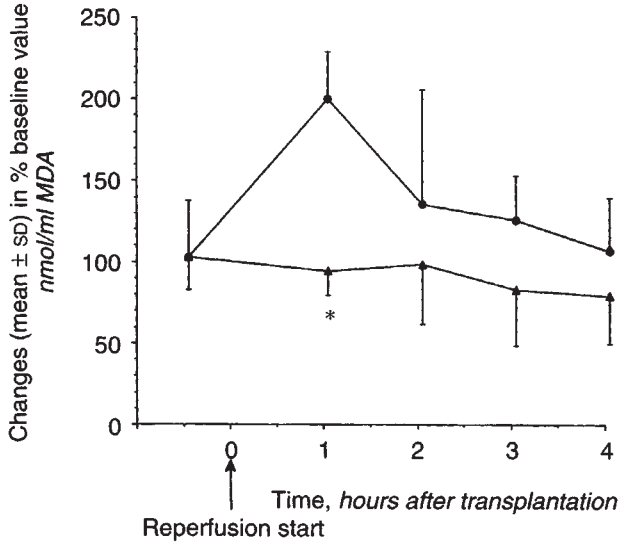

Fig. 1. *Time course of the change of plasma MDA values measured in kidney allograft recipients with (▲, N = 16) and without (●, N = 14) treatment with Omnibionta.* MDA values were determined 0.5 hr prior to start of reperfusion and at the indicated time points after begin of reperfusion. The bars give the standard deviation. * $P < 0.0001$.

significantly better renal function during the first days after transplantation than the control group, is also evident from the creatinine clearance (Table 3). At the postoperative days 1, 3 and 5, the creatinine clearance rate was significantly improved with $P < 0.03$ to 0.01 and 0.007, respectively. For example, at days 1 and 3 the creatinine clearance was about threefold better than in the control group.

Finally we have also examined whether statistical differences existed between the control and therapy groups, regarding age of the patients and duration of the storage time of the transplanted kidney. No statistical significant difference existed in these two parameters. Also the type of preservation medium in which the kidney was stored until transplantation had no effect on MDA values, creatinine or creatinine clearance. Further factors were compared which could lead to delayed allograft function such as pre-missmatch, age and cause of death, hypotension, administered pressors and serum creatinine in donors, the number of transplantations and required dialysis in recipients. A difference could only be computed for the serum creatinine values in donors, which was significantly lower for the control than for the therapy group ($P < 0.018$, mean ± SD 0.85 ± 0.22 vs. 1.17 ± 0.38 mg/dl).

Discussion

Reperfusion of an ischemic organ often results in severe tissue damage, which is in part the consequence of reoxygenation rather than the ischemic episode itself. Various lines of research at the biochemical level and animal experiments suggest that reoxygenation leads to an overproduction of deleterious oxygen radicals, which overwhelm the natural antioxidant defense and impose an increased oxidative stress on the reperfused organ and possibly on the whole body.

We have previously found [39] that surgical revascularization operations in humans for limb salvage (28 cases) or kidney transplantation (9 cases) shortly after start of reperfusion causes a strong increase of lipid peroxidation, as measured by plasma malonaldehyde. In continuation of this study further measurements in additional five kidney recipients were made. Table 1 contains all 14 controls examined so far, including some additional information (preservation time and solutions) not given in the cited reference [39]. Compared to the initial baseline values (= 100%) the one hour MDA increased in kidney transplantation to 197% (Fig. 1). In the case of limb revascularization (individual data reported in [39]) the MDA increased to 153%.

At the first glance, a mean increase of plasma peroxides from 0.74 to 1.46 nmol MDA/ml (Table 1) may appear to not be

Table 2. MDA values determined by HPLC in plasma of patients receiving kidney allograft and treated by intravenous infusion of omnibionta (therapy group)

Patient number	Age *years*	Kidney		MDA *nmol/ml plasma*								
		Preservation hr	Solution	−0.5 hr	1.0 hr	2.0 hr	3.0 hr	4.0 hr	1 day	2 day	3 day	4 day
1	37	18.5	EC	0.94	0.76	0.64	0.76	0.70	0.94	0.88	1.93	2.85
2	30	12.2	UW	1.01	0.72	0.89	0.97	0.81	1.19	0.86	1.27	2.04
3	54	6.4	EC	1.27	1.31	1.11	1.01	—	0.91	1.03	—	—
4	38	33.2	UW	0.87	0.87	0.71	0.60	0.54	0.46	0.50	0.83	0.79
5	24	19.5	HTK	0.69	0.62	0.52	0.53	—	0.67	0.44	0.85	0.84
6	29	25.2	EC	0.87	0.93	0.74	—	0.69	—	1.17	—	—
7	33	30.5	UW	0.73	0.47	0.40	0.37	0.44	—	—	—	—
8	31	11.0	HTK	0.78	1.09	0.73	0.82	0.92	—	—	—	—
9	57	9.4	UW	0.99	1.11	1.42	1.03	1.08	—	—	—	—
10	21	34.4	EC	0.62	0.38	0.35	0.41	0.29	—	—	—	—
11	46	21.0	UW	0.88	0.67	0.59	0.70	0.73	0.38	0.48	0.71	0.67
12	63	18.0	EC	1.24	1.02	0.91	0.66	0.98	0.68	0.67	0.95	0.85
13	63	30.5	EC	1.12	0.88	3.10	0.79	0.50	—	—	—	—
14	52	5.0	UW	1.23	0.88	0.63	0.82	—	0.70	0.71	0.59	0.45
15	31	6.0	UW	0.96	1.13	1.08	1.06	1.05	—	—	—	—
16	56	14.2	EC	1.06	1.15	0.75	0.88	0.86	0.69	0.85	1.01	1.55
Mean	41.45	18.43		0.953	0.856	0.764	0.760	0.738	0.736	0.759	1.018	1.255
±SD	14.14	9.97		0.197	0.257	0.282	0.216	0.244	0.248	0.243	0.421	0.827

Abbreviations are in Table 1.

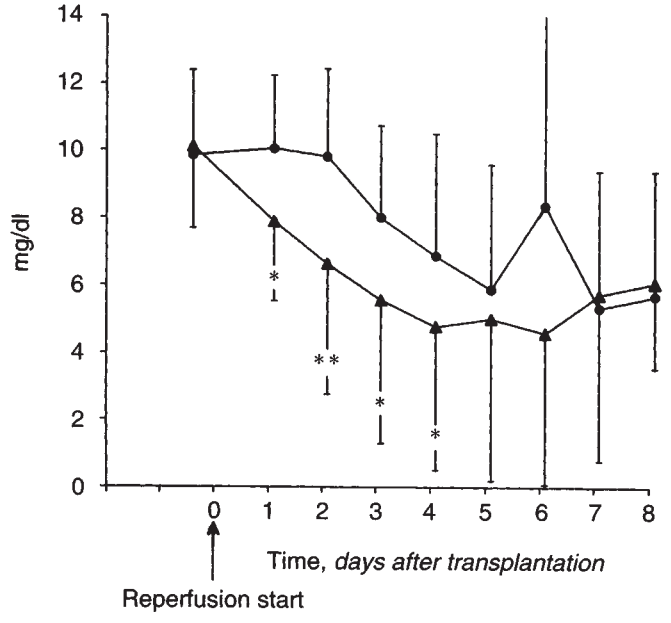

Fig. 2. *Time course of mean serum creatinine levels measured in kidney allograft recipients with (▲, N = 16) and without (●, N = 14) treatment with Omnibionta.* Values were measured preoperatively (0 day value) and at the indicated days after transplantation. The bars give the standard deviation. * $P < 0.02$; ** $P < 0.006$.

dramatic. This increase should, however, be compared with results from experimental animal studies. For example, in rats poisoned with $NiCl_2$, a compound inducing severe lipid peroxidation in lung, liver and kidney, plasma MDA values (measured with the same assay as used in this study) increased from 1.4 to about 2.1 to 2.5 nmol/ml [42]. Thus a doubling of plasma MDA, as seen in our kidney transplanted patients (Fig. 1, Table 1), indeed reflects a massive lipid peroxidation. It is reasonable to assume that the plasma lipid peroxides stem from oxidatively destroyed membranes of the perfused and reoxygenated kidney. The rapid (within a few hours) return of plasma lipid peroxides to the baseline level indicates that peroxidation in the perfused kidney was a short-lasting and transient event. The reason for that might be that lipid peroxidation was restricted to certain foci (such as endothelial cells) where all susceptible polyunsaturated fatty acids were quickly oxidized. Otherwise, it could be that the plasma antioxidants entering into the kidney from the reflowing blood halted the lipid peroxidation chain reaction. From the few patients where plasma MDA values have also been examined on the third and fourth days after transplantation, the majority had higher values compared to the first and second days after transplantation, suggesting a second phase of lipid peroxidation. A similar observation of a late increase of MDA was recently reported for patients with myocardial infarction [44].

Allpurinol [20–22], superoxide dismutase or catalase have been used with some success to reduce oxygen radical mediated reperfusion injury [reviewed in 45]. Inhibition of lipid peroxidation by low molecular weight lipid or water soluble antioxidants has not received very much attention so far, although it might be one of the most immediate approaches for therapeutic treatment of humans.

From the time course of lipid peroxidation after kidney transplantation (Fig. 1), it is clear that a successful prevention will only be possible if the antioxidants are administered prior to or immediately at the start of reperfusion. In kidney transplantation, where rapid decisions have to be made, oral supplementation prior to surgery is impracticable. We therefore opted for an intravenous infusion during the operation itself, but started it prior to the start of reperfusion of the transplanted organ. In Austria, the only antioxidant preparation approved and registered for intravenous infusion is Omnibionta; we have therefore decided to examine its potentially beneficial effects in kidney transplantation.

As can be seen in Table 2 and Figure 1, treatment with Omnibionta fully prevented the reperfusion mediated rise of

Table 3. Statistical comparison of control and therapy groups

	Control (N = 14)		Therapy (N = 16)		Statistical difference from control (P)
	Mean ± SD	Range	Mean ± SD	Range	
Age, *years*	43.0 ± 9.86	27–56	41.6 ± 14.1	21–63	NS
Preservation time of kidney, *hr*	24.12 ± 8.73	5–38.5	18.4 ± 9.9	5–34	NS
MDA, *nmol/ml plasma*					
0.5 hr before reperfusion	0.74 ± 0.26	0.32–1.20	0.95 ± 0.19	0.62–1.24	0.03
1.0 hr after reperfusion	1.46 ± 0.22	1.11–1.84	0.85 ± 0.25	0.38–1.15	<0.0001
Creatinine *mg/dl serum*					
preoperative	9.7 ± 2.16 (12)	5.3–13.8	9.9 ± 2.2 (14)	6.2–13.9	NS
1 day after transplantation	9.91 ± 2.15 (14)	7.3–14.8	7.7 ± 2.4 (16)	4.0–13.0	<0.02
2 days after transplantation	9.66 ± 2.62 (14)	6.1–13.9	6.5 ± 3.8 (16)	2.0–16.3	<0.006
Creatinine clearance, *ml/min*					
1 day after transplantation	12.13 ± 6.24 (9)	2.1–20.5	39.3 ± 36.7 (11)	1.7–107	<0.03
3 days after transplantation	15.65 ± 12.65 (9)	2.1–36.9	41.7 ± 23.3 (11)	10.7–82	<0.01
5 days after transplantation	26.3 ± 19.5 (9)	1.6–54.6	59.5 ± 21.7 (8)	16.4–79	<0.007
7 days after transplantation	32.15 ± 29.15 (8)	1.2–80.0	58.8 ± 23.0 (3)	32.3–74	NS

Control group was comprised of 14 patients and 16 patients were in the therapy group; if not all patients were examined, their number is given in (brackets).

plasma lipid peroxides. Even more importantly, in the first four to five days after transplantation the patients of the therapy group had a much better renal function, as is clearly indicated by the significantly ($P < 0.02$ to 0.006) lowered serum creatinine levels (Fig. 2) and the three- to fourfold better ($P < 0.007$ to 0.01) creatinine clearance rate. This finding suggests, but of course does not prove, a causal relationship between lipid peroxidation and renal reperfusion injury, or in other words, that inhibition of lipid peroxidation resulted in improved viability and function of the transplanted kidney. After about the fifth postoperative day the renal performance of the therapy and control groups approached each other, and from thereon no statistically significant difference between the two groups existed.

Can the effects of Omnibionta indeed be ascribed to an antioxidant effect, and if so, to which one of the antioxidants? This question is difficult to answer, since Omnibionta contains additional to the antioxidant vitamins, that is, ascorbate (vitamin C), α-tocopherol (vitamin E) and retinol (vitamin A), and several components of the vitamin B-complex (vitamin B_1, vitamin B_2, niacin and panthotenate). The administered dose (2 ampoules) of the individual vitamins corresponds to the x-fold of the daily requirement recommended by the German Society for Nutrition [46]: ascorbate 13x, vitamin E 1.0x, vitamin A 6x, vitamin B_1 70x, vitamin B_2 8x, niacin 11x, vitamin B_6 16x and panthotenate 6x. With the simplified assumption that the antioxidant vitamins distributed during infusion solely in the blood serum compartment, they reached there peak concentrations of about 2.3 mM (ascorbate), 10 μM (vitamin E) and 8 μM (vitamin A), which has to be compared with the estimated normal levels (not measured) of approximately 40 μM ascorbate, 20 μM vitamin E and 1 μM vitamin A. This rough estimation suggests that the infused ascorbate plays a major role in inhibiting lipid peroxidation. Of all the antioxidants ascorbate had the strongest relative increase (about 50-fold) and reached the highest concentration (about 2.3 mM) in plasma. The infusion mediated change of the endogenous levels of vitamin E and A was much less than that of vitamin C. The inhibitory effects of ascorbate on lipid peroxidation are well documented: it essentially protects vitamin E, the primary membrane antioxidant, against destruction by free radicals. Infusion of a high concentration of ascorbate presumably prevents lipid peroxidation by improving the recycling of vitamin E. The other components of the vitamin B complex could have an important auxiliary function in stimulating metabolic pathways providing reducing equivalents (NADPH) necessary to keep glutathione and ascorbate in the reduced form. That ischemia reperfusion shifts the GSH/GSSG equilibrium to the side of GSSG has been reported by Ferrari et al [47].

Finally, it should be mentioned that ischemia reperfusion causes the production of different humoral mediators, including thromboxane A_2, prostaglandins and leukotrienes. Thromboxane A_2 is a potent vasoconstrictor and platelet proaggregator, whose level increases after ischemia in different organs. A blockage of thromboxane A_2 formation has been found to improve kidney performance after ischemia [45]. According to Lands, Kulmacz and Marshall [48], plasma and tissue "peroxide tone" is an important factor in regulating eicosanoid homeostasis. A normal peroxide tone, as achieved by treatment with Omnibionta, may therefore also contribute to better the renal vascular function.

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